IN THE SPECIFICATION

Please amend the specification on page 7, lines 18-26 as follows.

Figure 1 shows the proposed topology of GPCR-B3, with a large extracellular domain extending from amino acid 1 to about amino acid 580 of the rat GPCR-B3 amino acid sequence (corresponding to nucleotide residues 1-1740 of the rat sequence, with the ATG initiator methionine defined as residue 1), and seven transmembrane domains. The large extracellular domain may extend into the first transmembrane domain. Dark residues indicate identities between GPCR-B3 and GPCR-B4 (for a description of GPCR-B4, *see, e.g.*, US Patent No. 6,383,778; *see also* Hoon *et al.*, *Cell* 96:541-551 (1999)).

IN THE CLAIMS

Please cancel claims 3, 9, 12, 14, 15, and 16.

Please amend claims 1, 10, 11, 17, 61, 62, and 63 as follows.

1. (twice amended) An isolated nucleic acid encoding a taste transduction G-protein coupled receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS, and wherein the nucleic acid encodes a receptor that has G protein coupled receptor activity.

10. (twice amended) An isolated nucleic acid encoding a taste transduction G-protein coupled receptor, wherein the nucleic acid selectively hybridizes under moderately stringent hybridization conditions to a nucleotide sequence of SEQ ID NO:4, SEQ ID NO:5 or

SEQ ID NO:6, wherein the hybridization reaction is incubated at 37°C in a solution comprising 40% formamide, 1M NaCl and 1% SDS and washed at 45°C in a solution comprising 1x SSC, and wherein the nucleic acid encodes a receptor that has G protein coupled receptor activity.

11. (twice amended) An isolated nucleic acid encoding an extracellular domain of a taste transduction G-protein coupled receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions to a nucleic acid encoding amino acids 1-563 of SEQ ID NO:1, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS, and wherein the nucleic acid encodes the extracellular domain linked to a nucleic acid encoding a heterologous receptor polypeptide, forming a chimeric receptor polypeptide that has G protein coupled receptor activity.

C3 cont

17. (twice amended) An isolated nucleic acid encoding a cytoplasmic domain of a taste transduction G protein coupled receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions to a nucleic acid encoding amino acids 812-840 of SEQ ID NO:1, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS and wherein the nucleic acid encodes the cytoplasmic domain linked to a nucleic acid encoding a heterologous receptor polypeptide, forming a chimeric receptor polypeptide that has G protein coupled receptor activity.

C4

61. (twice amended) A method of making a taste transduction G-protein coupled receptor, the method comprising the step of expressing the receptor from a recombinant expression vector comprising a nucleic acid encoding the receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS

C5

and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS, and wherein the nucleic acid encodes a receptor that has G protein coupled receptor activity.

62. (twice amended) A method of making a recombinant cell comprising a taste transduction G-protein coupled receptor, the method comprising the step of transducing the cell with an expression vector comprising a nucleic acid encoding the receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS, and wherein the nucleic acid encodes a receptor that has G protein coupled receptor activity.

C5 Cont

63. (twice amended) A method of making an recombinant expression vector comprising a nucleic acid encoding a taste transduction G-protein coupled receptor, the method comprising the step of ligating to an expression vector a nucleic acid encoding the receptor, wherein the nucleic acid specifically hybridizes under highly stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS, and wherein the nucleic acid encodes a receptor that has G protein coupled receptor activity.

REMARKS

With this amendment, claims 1, 4-6, 8, 10, 11, 13, 17, 18, 34, 35, and 61-63 are pending in the application. Claims 3, 9, 12, 14, 15, and 16 have been canceled. Appendix A provides the "Version with Markings to Show Changes Made." All pending claims are provided in Appendix B for the Examiner's convenience.

Objection to the specification

The specification has been amended to delete patent application serial numbers and to recite the corresponding issued US Patent. Applicants respectfully request that the objection be withdrawn.

Status of the claims

Claims 1, 10, 11, 17, 61, 62, and 63 have been amended to recite specific hybridization conditions. These amendments add no new matter. Support for these amendments can be found, e.g., in the specification on page 23, lines 16-18 and 23-25.

Claims 1, 10, 11, 17, 61, 62 and 63 have been amended to recite a nucleic acid encoding a polypeptide that has "G protein coupled receptor activity." This amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the specification on page12, lines 5-10 and page 13, lines 22-30.

Claims 11 and 17 have been amended to recite a "chimeric receptor polypeptide." This amendment adds no new matter. Support for this amendment can be found, e.g., in the specification on page 5, lines 23-24, page 6, lines 17-19, page 8, lines 1-4 and page 42, lines 18-24.

Rejection under 35 U.S.C. § 101

Claims 1, 3-6, 8-18, 34, 35, and 61-63 were rejected as allegedly supported neither by a specific, substantial, and credible utility, nor by a well-established utility. The rejection states that "the proposed use of the polypeptide to screen for ligands of the polypeptide or for biologic effects of the polypeptide is not a substantial utility." Office Action, page 3, lines 9-11.

Applicants respectfully traverse the rejection. Applicants have disclosed in the present specification that the claimed nucleic acid, a full length cDNA, encodes a G protein coupled receptor ("GPCR-B3") that is specifically expressed in taste buds of the tongue, and have provided data demonstrating that the claimed protein is a functional G-protein coupled

receptor. The present invention is therefore useful, e.g., assays to identify taste ligands of the claimed GPCR, for modulation of taste. Applicants herewith present a declaration of Dr. Charles Zuker pursuant to 37 C.F.R. § 1.132, which describes that one of skill in the art would easily recognize a "substantial" or "real world" utility for the claimed nucleic acids.

According to the MPEP, in order to assess utility, the Examiner should review the specification to determine if there are any statements asserting that the claimed invention is useful for any particular purpose. An invention has utility if the utility is specific, substantial and credible. A utility is specific if it is specific to the subject matter claimed. A utility is substantial if it has a real-world use. In most cases, an applicant's assertion of utility creates a presumption of utility that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Furthermore, an Examiner cannot simply dismiss an assertion of a particular utility as wrong but must determine if the assertion is credible, i.e., would be believable to a person of ordinary skill in the art based on the totality of the evidence (*see* MPEP § 2107.02).

In his declaration, Dr. Zuker explains why one of skill in the art would recognize the utility of the present invention. Dr. Zuker's resume is attached hereto as Exhibit A. As described in the present specification and in the Declaration, full length cDNAs that encode a taste cell-specific nucleic acids were cloned. Sequence analysis of the GPCR-B3 clone showed that it had the structure of a G-protein coupled receptor, with an extracellular domain, seven transmembrane domains, and a cytoplasmic domain (*see, e.g.*, Example I, page 56-57). Subsequently, protein expression patterns were determined for GPCR-B3 using *in situ* analysis (*see, e.g.*, Example II, page 58, and Figure 3). Figure 3 shows that the claimed nucleic acids express proteins that are specifically expressed in taste buds of the tongue.

Furthermore, the specification provides experimental data demonstrating that GPCR-B3 is a functional G-protein coupled receptor. Figure 4 shows the structure of a chimeric protein, comprising an extracellular domain of a murine MGluR1 receptor fused to the seven transmembrane domains and cytoplasmic domains of GPCR-B3. This chimeric GPCR construct was transfected into HEK cells, which were then stimulated with glutamate, the MGluR1 ligand. The HEK cells demonstrated an increase in intracellular calcium in response to the ligand,

indicating that the chimeric GPCR couples to a promiscuous G protein and triggers calcium responses that are detectable using the indicator fura-2. The presently claimed "GPCR-B3" nucleic acids therefore encode a G protein coupled receptor that is specifically expressed in fungiform and foliate cells of the tongue, which are taste bud cells, as described in the specification.

According to Dr. Zuker, it would be apparent to anyone of skill in the art that GPCR-B3 is an excellent target for candidate compounds that modulate taste transduction. This use is not merely a "starting point for further research and investigation," but a direct assay for taste ligands and modulators of taste signal transduction. Furthermore, the claimed nucleic acids are specifically expressed in a unique subset of tongue cells, and the encoded proteins localize to the taste pore--the subcellular location for taste receptors. As such, they have specific and substantial utility as markers for specialized taste cells of the tongue. Such markers are useful for the generation of taste topographic maps the elucidate the relationship between taste bud cells of the tongue and taste sensory neurons leading to taste centers in the brain. Applicants have therefore provided a nucleic acid that encodes a protein with known signaling activity and specific expression in a specialized sub-set of cells. The nucleic acids of the invention therefore have specific, substantial, and credible utility. Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: enablement

Claims 1, 3-6, 8-18, 34, 35, and 61-63 were rejected as allegedly lacking enablement, as the claimed invention is allegedly supported neither by a specific and substantial asserted utility, nor by a well established utility. Applicants respectfully traverse the rejection. As described above, the instant claims are well supported by a specific and substantial asserted utility. As the Examiner has provided no other reasoning why the claims lack enablement, Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: written description

Claims 1, 3-6, 8-18, 34, 35, and 61-63 were rejected as allegedly containing subject matter that was not described in the specification as originally filed. Applicants respectfully traverse this rejection. The claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

Applicants respectfully note that the written description requirement is directed to description of a genus by structural features. The Examiner, however, has also required recitation of a functional feature in addition to the claimed structural features. In the Office Action, the Examiner observed that "no particular functional limitations for the encoded polypeptides are required by the claims which might limit the genus to that which is adequately described." Office Action, page 5, lines 16-18. Furthermore, with regard to the claimed structural features, the Examiner states that "no particular structural features are required of the members of the genus and there are no functional elements that link the vast number of disparate members of this genus. Office Action, page 6, lines 6-8.

The claims set forth both functional elements as well as structural elements, i.e., hybridization conditions and reference sequences to which members of the claimed genus hybridize. Therefore, the claimed sequences are thereby defined via shared physical and structural properties.

As described above, the present invention relates to the discovery of a nucleic acid encoding a new taste bud specific GPCR, called GPCR-B3. The genus of GPCR-B3 nucleic acids and the proteins that they encode is claimed by reference to shared structural features, i.e., nucleic acid sequences (SEQ ID NO:4, 5, or 6) that encode either the entire GPCR-B3 protein

(SEQ ID NO:1, 2 or 3) or conserved structural domains of the GPCR-B protein (e.g., extracellular or cytoplasmic domains). The claims also provide hybridization conditions in which the claimed genus of GPCR-B3 nucleic acids hybridize to the reference conserved sequences. Finally, the GPCRs are claimed by reference to shared functional features, i.e., taste specific expression and GPCR activity.

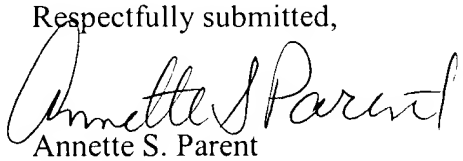
The ability of a particular nucleic acid to hybridize under *given conditions* to a reference nucleic acid is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule (*see, e.g.*, Sambrook, *Molecular Cloning: A Laboratory Manual*, pp. 9.47-9.51 (2nd ed. 1989); *see also* Stryer, *Biochemistry*, pp. 573 (2nd ed. 1975)). As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*).

In the present application, Applicants have provided both reference nucleotide sequences, as well as hybridization conditions. As required by the standard set forth in *University of California v. Eli Lilly*, these structural features are common to all of the members of the GPCR-B3 polypeptide genus. The conserved sequences encoding structural features of the genus, and the given conditions under which the claimed genus would hybridize to such reference sequences or have a specified identity to such sequences "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). The specification thus appropriately describes the claimed GPCR-B3 nucleic acid and protein genus using structural/physical features, as required by the court in *University of California v. Eli Lilly*. Furthermore, the claims recite functional features of the genus. As such, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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